Taste function in early stage treated and untreated Parkinson's disease

AUTHOR'COPY

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Abstract

Since brain stem regions associated with early Parkinson's disease (PD) pathology encroach upon those involved in taste function, the ability to taste may be compromised in PD. However, studies on this point have been contradictory. We administered well-validated whole- mouth and regional taste tests that incorporated multiple concentrations of sucrose, citric acid, caffeine, and sodium chloride to 29 early stage PD patients and 29 age-, sex-, and race-matched controls. Electrogustometry was also performed on the anterior tongue. The PD cohort was tested both on and off dopamine-related medications in counterbalanced test sessions. While whole-mouth taste identification test scores for all stimuli were, on average, nominally lower for the PD patients than for the controls, a trend in the opposite direction was noted for the intensity ratings at the lower stimulus concentrations for all stimuli except caffeine. Moreover, regional testing found that PD subjects tended to rate the stimuli, relative to the controls, as more intense on the anterior tongue and less intense on the posterior tongue. No significant associations were evi- dent between taste test scores and UPDRS scores, L-DOPA medication equivalency values, or [99mTc]TRODAT-1 SPECT imaging of dopamine transporter uptake within the striatum and associated regions. Our findings suggest that suprathreshold measures of taste function are influenced by PD and that this disease differentially influences taste function on anterior (CN VII) and posterior (CN IX) tongue regions. Conceivably PD-related damage to CN IX releases central inhibition on CN VII at the level of the brainstem, resulting in enhanced taste intensity on the anterior tongue.

Introduction

Parkinson's disease (PD), the second most common neu- rodegenerative disease, afflicts more than six million peo- ple worldwide [1]. Although the cardinal features of this chronic disorder are motor system related, e.g., tremor, rigidity, bradykinesia, and postural instability, PD is asso- ciated with numerous non-motor disturbances, including alterations in olfaction, vision, balance, and cognitive function [2]. However, most such disturbances have received comparatively little study, despite their significant impact on quality of life. In one international multi-center survey of non-motor symptoms of PD patients, complaints concerning smell and taste were among the most frequent: 26 % of the patients complained of problems tasting or smelling, compared to only 7.3 % of a control group [3].

Unlike olfaction, whose dysfunction occurs in nearly all PD patients [4], the degree to which PD influences taste function is poorly understood. Importantly, it is unknown whether taste testing may be of value, like olfactory testing, in detecting early stage PD. The region of the brainstem associated with taste, i.e., the nucleus tractus solitarius (NTS), is not far removed from brainstem regions where Lewy body pathology first appears [5, 6] and structural and resting state functional imaging studies have found reduced activity between the entire extended brainstem and the striatum in patients with PD [7]. Nevertheless, evidence for Lewy body pathology within the NTS itself is scant [8].

The few studies that have evaluated taste function in PD have produced inconsistent results. In a pioneering study, Sienkiewicz-Jarosz et al. [9] tested 30 medicated PD patients and 33 healthy controls for their ability to identify and rate the intensity and pleasantness of citric acid (sour), NaCl

(salty), quinine (bitter) and sucrose (sweet) presented on filter paper strips to the tip of the tongue. Electrical thresholds were obtained from the same tongue area. No PD-related deficits in the intensity or pleasantness ratings were found. Surprisingly, the PD patients rated, on average, a 0.025 % concentration of quinine as more intense than did the controls (p \ 0.04) and exhibited lower electrical taste thresholds (p \ 0.001). Although a subsequent study of 20 PD patients and 20 age-matched controls by this group did not replicate the electrogustometric finding, a 1 % solution of sucrose presented by syringe to the anterior tongue was rated as more intense by the PD patients than by the controls [10]. No influences of PD on whole-mouth pleasantness ratings of sucrose solutions were observed in this study.

In contrast to the work of Sienkiewicz-Jarosz et al. are studies reporting at least some PD-related decrements in taste function. Travers et al. [11] had 25 PD patients and 16 normal controls rate the pleasantness of six ascending su- prathreshold concentrations of sucrose on a six-point rating scale. The preference curve of the PD subjects was a monotonically increasing function, whereas that of the controls was an inverted U-shape, peaking at the 0.3 M concentration. Conceivably the PD patients perceived the higher sucrose concentrations as weaker and therefore did not experience them as less pleasant. Lang et al. [12] found, on average, that 10 patients with Parkinson syn- drome [6 with PD, 1 with PD and Alzheimer's disease (AD), and 3 with Lewy body dementia] had more difficulty than 42 assorted patients without dementia in identifying sour and salty sensations from citric acid and NaCl embedded on filter paper strips. Unfortunately, these comparisons were confounded by varying degrees of dementia within the Parkinson syndrome group and the use of a heterogeneous group of controls, some of whom had prior ''minor strokes'' or who had vascular risk factors for stroke. More recently, Moberg et al. [13] noted that only 24 % of 56 PD patients could detect the bitter taste of phenylthiocarbamide (PTC), as compared to 75 % of 20 healthy controls. Kim et al. [14] found a marginal decrease in identification performance of 15 women with PD rela- tive to 14 female controls when the data were combined across sweet, sour, bitter and salty tastants. However, the effects were not significant when any one taste quality was assessed alone. Cecchini [15] reported that 61 PD patients were less able, on average, than 66 controls to accurately identify the salty taste of NaCl presented on a piece of filter paper, although this was not the case for sweet, sour, and bitter tasting stimuli. No deficit was apparent when the NaCl was sprayed into the mouth. In a large study, Shah et al. [16] found that *27 % of 75 PD patients had impaired taste function relative to 74 age- and sex-matched controls, as measured by electrogustometry. The thresholds were elevated on both the front and back of the tongue and were not influenced by PD-related medications.

In light of the aforementioned disparities and the limited amount of information on this topic, the present study sought to more definitively establish the influences of PD on taste function. Early stage PD patients and healthy age- and sex-matched controls were administered electrical and whole-mouth and regional chemical taste tests in a within subjects design in which the same cohort of PD patients was tested while on and off dopamine-related medications (DRMs). Our use of early stage patients was predicated on understanding whether the taste deficits of PD, if present, might be useful in early diagnosis of the disorder. A determination was also made as to whether the test scores were related to the side of major motor disturbance, disease duration, gender, scores on the United Parkinson's Disease Rating Scale (UPDRS), and single-photon emission com- puted tomographic (SPECT) imaging of the dopamine transporter (DAT) within the basal ganglia.

Materials and methods

Subjects

Fifty-eight subjects participated (Table 1). Half were early stage PD patients [mean (SD) Hoehn & Yahr (H&Y) score = 1.4 (0.5)] [17] and half healthy age-, sex- and race-matched controls. None exhibited significant cogni- tive dysfunction (MMSE scores C28). All patients had lateralized motor deficits and a history of motor symptoms \2 years and met the Gelb et al. [18] criteria for PD. They were recruited from news media advertisements as well as from multiple neurological clinics throughout the Phila- delphia region, whereas the controls were obtained via fliers posted on the campus of the University of Pennsyl- vania, by word of mouth, and from news media. Most of the patients were referred to the study from the Parkinson's and Movement Disorders Center of Pennsylvania Hospital and the Hospital of the University of Pennsylvania. Others were referred from neurology clinics at the Thomas Jefferson University Medical Center in Philadelphia, the Veterans Administration Hospital of Philadelphia, and the Crozer-Chester Medical Center in Chester, Pennsylvania. Each patient was diagnosed by one of the project's movement disorders specialists, as well as by the patient's own neurologist. The normal controls underwent the same neurological examinations as the patients and met the same exclusion criteria. All controls were found to be normal neurologically and none had a first degree relative with any type of neurodegenerative disease.

Because this study was a component of a comprehensive program that evaluated auditory, gustatory, olfactory, tac- tile, vestibular, and visual function in the same cohort of early stage PD patients, the exclusion criteria were designed to minimize the likelihood of confounding factors that could adversely influence the results of any of these components of the study. They included a history of alcohol or substance abuse, stroke, brain tumor, vascular abnormalities, rhinosinusitis, seizure disorder, multiple sclerosis, Bell's palsy, brain aneurysm, encephalitis, sig- nificant head trauma, drug abuse, otosclerosis, acoustic neuromas, Meniere's disease, Usher's syndrome, glau- coma, oculogyric crises, psychiatric disorders (e.g., dementia, schizophrenia, chronic or major depression, psychosis, bipolar disorder, anorexia, Asperger's syn- drome), supranuclear gaze palsy other than restricted up gaze, cerebellar signs, early severe autonomic involvement, Babinski sign, allergies, a current or prolonged upper respiratory infection, or any other non-PD-related condi- tion that could reasonably be expected to interfere with the numerous study assessments. Women of child-bearing potential were required to have a negative pregnancy test within 2 days before the SPECT imaging. The study pro- tocol was approved by the Office of Regulatory Affairs of the University of Pennsylvania and the study was con- ducted in accordance with the principles of the Declaration of Helsinki. All subjects provided informed written consent for participation. Each subject was paid $1,200 for partic- ipation in the entire program.

Experimental design

The entire study, of which the taste testing was just a part, occurred during two 4-day-long test periods. During one period the PD patients had been taking DRMs for at least 6 weeks, whereas during the other they were unmedicated. The order of the on- and off-DRM test periods was coun- terbalanced, with approximately half of the patients being on DRM during the first period and the other half off DRM during this period. The patients initially tested under the no-DRM condition were de novo patients who had never received DRMs. Those patients who were on carbidopa/ levodopa during the first test period were required to stop

their medication at least 15 h before the off-DRM test period, whereas those who were taking either of the dopamine agonists were required to stop their medication at least 72 h before the off-DRM period. During the on- DRM period, 17 of the patients were taking carbidopa/ levodopa 25/100, 9 were taking the dopamine agonist pramipexole, and 2 were taking the dopamine agonist ro- pinirole. Twenty-three PD patients completed both the DRM and non-DRM sessions; six completed only one of the two sessions, reflecting either a desire not to go through the test sequence again or a problem with medication ini- tiation or discontinuance. The controls were tested at the same general time points as the PD patients and received same tests, including the SPECT imaging. They did not, however, take DRMs.

Taste test measures

Three taste tests were administered by trained test exam- iners. In the whole-mouth test, 10 mL samples of five different suprathreshold concentrations of sucrose (0.08, 0.16, 0.32, 0.64, 1.28 molar [M]), sodium chloride (0.032, 0.064, 0.128, 0.256, 0.512 M), citric acid (0.0026, 0.0051, 0.0102, 0.0205, 0.0410 M), and caffeine (0.0026, 0.0051, 0.0102, 0.0205, 0.0410 M) were presented in small cups to the subjects in a counterbalanced order [19]. Each solution was sipped, swished in the mouth, and expectorated. The subject indicated, in a forced-choice paradigm, whether a given solution tasted sweet, salty, sour, or bitter, and rated its intensity and unpleasantness/pleasantness on 9-point rating scales, with the larger values representing greater intensity and pleasantness, respectively. After responding, the subjects rinsed their mouths with purified water. Forty stimulus presentations were administered (4 tastants 9 5 concentrations 9 2 trials). The possible identification score for a given tastant was 10. In the regional taste test, suprathreshold taste function was assessed on the left and right sides of the anterior and posterior tongue. The target tongue regions were close to the lateral margins of the anterior tongue and in close proximity to lateral circum- vallate papillae in the posterior part of the tongue. For each tongue region, 15 ll of sucrose (0.49 M), sodium chloride (0.31 M), citric acid (0.015 M), and caffeine (0.04 M), equated for kinematic viscosity using cellulose (*1.53 mm2/s), were presented in a counterbalanced order using a micropipette (Eppendorf, Hamburg, Germany). On a given trial, a subject reported whether the solution tasted sweet, sour, salty, or bitter and rated its perceived intensity on a segmented visual analog scale with the extremes labeled as very weak and very strong and with a back- ground logarithmic gradation of shading (see [20], p. 80) before retracting the tongue and rinsing with purified water. A total of 96 forced-choice trials (4 tastants 9 4 lingual regions 9 6 repetitions) was presented. The maximum identification score each subject could achieve for a given tastant was 24. In the electrogustometry test, the lowest anodal current that could be discerned from 6.4 lA (0.5 s duration) was determined using the TR-06 Rion electro- gustometer (Rion Co., Tokyo, Japan) using an initially ascending forced-choice single staircase test procedure. Testing was performed on the left and right sides of the anterior tongue in a counterbalanced order and a sequential two-down, one-up rule of stimulus presentation was fol- lowed, with the exception that five consecutive correct responses had to be made to induce the first staircase reversal. The mean of the last four of seven staircase reversals was used as the threshold estimate. In cases where the first reversal occurred at 10 lA or the staircase converged at this point, i.e., one step higher than the comparison stimulus, a value of 6.4 lA was assigned as the threshold estimate.

TRODAT Technetium-99 m SPECT brain imaging

Dopamine transporter uptake within the striatum and associated regions was assessed using Technetium-99 m TRODAT [21–23]. For each measurement, 20.0 ± 2 mCi of TRODAT was intravenously administered. Following at least three but not more than 4 h of biodistribution time, imaging was performed using a Siemens SymbiaTM SPECT/CT with ultra-high resolution collimators. Imme- diately following acquisition of the SPECT images, a low- dose CT of the brain was obtained for anatomic localiza- tion and attenuation correction. Average counts per mm3 were obtained for six regions of interest (ROI) from each data set: left caudate nucleus, right caudate nucleus, left anterior putamen, right anterior putamen, left posterior putamen and right posterior putamen. Each Tc99m TRO- DAT distribution volume ratio (DVR) essentially repre- sents a punch biopsy of pre-synaptic dopamine transporter in a given region. A cortical background value was obtained from the right superior parietal lobule. DVRs were defined on the low-dose CT images blinded to the SPECT data to eliminate bias. Mean DVRs were calculated for each striatum ROI relative to cortical background using the following formula: DVR = (ROI - reference region)/ reference region.

Statistical analyses

The whole-mouth and regional taste test data were independently analyzed using analyses of variance (ANOVA) [24], as were those from each of the four tastants (sucrose, citric acid, caffeine, NaCl). Because of the skewed distributions of the electrical thresholds, only non-parametric analyses were performed on these measures, i.e., the Wilcoxin signed-ranks test for within subject comparisons and the Mann–Whitney U test for between subject comparisons [24]. For the whole-mouth tests, three dependent variables were assessed: (a) the percent correct identification performance, (b) the ratings of perceived intensity, and (c) the ratings of perceived unpleasantness/pleasantness. For the regional taste test, only the first two of these measures were evaluated since ratings of perceived hedonics were not obtained. The percent correct scores were arcsin transformed before being subjected to analysis. The data from the PD patients were initially assessed separately from those of the controls to address PD-specific questions; namely, the influences of side of major motor disturbance and DRMs. Since preliminary ANOVAs per- formed on the regional taste test data found no influence of tongue side on the test measures of either the PD or control subjects, the tongue side data were averaged, resulting in anterior (CN VII) and posterior tongue measures (CN IX). In the few cases where both sessions had not been completed, the single session's value was used in subsequent analyses. The within subject factors for the PD cohort were DRM condition (on, off), tongue region (regional test), and tastant concentration (whole-mouth test); the between subject factors were sex and side of major motor disturbance. The ANOVAs assessing PD vs. controls used the same factors, except that the DRM condition was replaced by the matched group factor (PD, control) and the side of major motor disturbance factor was omitted. Since a large number of the subjects correctly identified the highest three concentrations of sucrose, eliminating variance in some cells, only the three lowest sucrose concentrations were subjected to the percent correct identification analysis. For the chemical taste tests, Pearson correlation coefficients were computed between the dependent measures and the UPDRS scores, the SPECT DVRs, and the DRMs, as measured by L-DOPA equivalents [25]. Spearman correlations were computed between these measures and the electrical taste thresholds.

Results

Analyses confined to the PD cohort

As in olfaction, the taste test scores were independent of dopamine-related processes. Thus, the main effect of DRM condition was not significant for any taste test or for any tastant (all ps [0.15). The same was true for side of major motor disturbance. No significant correlations were evident

between any of the taste test measures and (a) the UPDRS scores, (b) disease durations, (c) the L-DOPA equivalency scores, or (d) the SPECT DVRs within the left and right side brain regions. As would be expected, the side of motor disturbance was associated with lateralized differences in [99mTc]TRODAT-1 uptake within the striatum, with less uptake on the side contralateral to the major motor dis- turbance (p \ 0.001).

The stimulus concentration factor was significant for al lwhole-mouth measures of the PD patients, reflecting con- centration-related changes in the test measures within each domain (identification: citric acid p = 0.027, g2 = 0.11; caffeine p \ 0.0001, g2 = 0.27; sodium chloride p \ 0.0001, g2 = 0.25; sucrose p = 0.035, g2 = 0.18; intensity ratings: citric acid p \ 0.0001, g2 = 0.68; caf- feine p \ 0.0001, g2 = 0.65; sodium chloride p \ 0.0001, g2 = 0.73; sucrose p \ 0.0001, g2 = 0.75; hedonic rat- ings: citric acid p B 0.0001, g2 = 0.29; caffeine p \ 0.0001, g2 = 0.60; sodium chloride p \ 0.001, g2 = 0.25; sucrose p = 0.003, g2 = 0.15).

In the regional taste tests, the stimuli were identified at a higher rate on the front than on the back of the tongue for all tastants except citric acid, as indicated by a significant tongue region main effect (front/back) (sucrose p \ 0.0001, g2 = 0.52; citric acid p = 0.82, g2 = 0.0012; caffeine p \ 0.0001, g2 = 0.40; sodium chloride p = 0.002, g2 = 0.32). Additionally, all four stimuli were rated as being more intense on the front than the back of the tongue (NaCl p \ 0.0001, g2 = 0.56; sucrose p \ 0.0001, g2 = 0.51; caffeine p \ 0.0001, g2 = 0.39; citric acid p \ 0.0001, g2 = 0.37).

Since the aforementioned concentration and tongue region effects proved not to be specific to PD, as described below, the summary statistics for these measures are combined with those of the control subjects in the following section.

Analyses comparing the PD and control group cohorts

Whole-mouth taste quality identification

The mean (SEM) percent correct identification values for the PD and control subjects for each stimulus concentration for the four taste stimuli are presented in Table 2. As shown in Fig. 1, the average values were nominally lower for the PD patients than for the controls for all tastants. However, a significant main effect of subject group (PD, controls) was present only for sodium chloride (p = 0.042, g2 = 0.14; all other ps [0.15). A significant group by concentration interaction was found for caffeine (p = 0.014, g2 = 0.11), but not for the other stimuli (all ps [0.20). This interaction reflected poorer taste identification performance by the PD patients at the lowest stimulus concentration (Fig. 2). The main effect of stimulus concentration was significant for each stimulus, reflecting a concentration-related increase in identification performance of the combined PD and control group sub- jects (citric acid p \ 0.0001, g2 = 0.19; caffeine p \ 0.0001, g2 = 0.23; sodium chloride p \ 0.0001, g2 = 0.45; sucrose p \ 0.0001, g2 = 0.29). No sex differences were apparent for any stimulus (all ps [0.10).

Whole-mouth taste intensity ratings

The mean (SEM) whole-mouth taste intensity ratings are presented in Table 3. As is apparent from the table, the ratings increased significantly across stimulus concentrations for all stimuli (citric acid p B 0.0001, g2 = 0.78; caffeine p \ 0.0001, g2 = 0.74; sodium chloride p \ 0.0001, g2 = 0.85; sucrose p \ 0.0001, g2 = 0.83). While the intensity ratings of the PD patients did not differ significantly from those of the controls for any taste quality (all ps [0.20), it is noteworthy that about a third (32.5 %) of the intensity ratings were nominally larger in the PD patients than in the controls. No sex differences were observed for any tastant (ps [0.10).

Whole-mouth taste hedonic ratings

The average whole-mouth hedonic ratings are shown in Table 4 for the PD and control subjects. The hedonic ratings monotonically decreased for sodium chloride, citric acid and caffeine across the increasing concentration gradients (citric acid 98.38, p B 0.0001, g2 = 0.78; caffeine p \ 0.0001, g2 = 0.74; sodium chloride p \ 0.0001, g2 = 0.85). For sucrose, such ratings increased as con- centration increased (p \ 0.0001, g2 = 0.83), although a reversal was evident at the higher stimulus concentrations, as expected from other research. Even though the 0.05 level of statistical significance was not reached in any case, the difference between the PD and control ratings of sodium chloride approached significance (p = 0.086, g2 = 0.46) (all other ps [0.15) and, of the 20 hedonic ratings, 85 % (17/20) were smaller for the PD patients than for their matched controls. Only the three lowest concen- trations of caffeine (bitter) were rated higher by the patients. The hedonic ratings fell within the pleasantness end of the 9-point rating scale ([4.5) only for sucrose. No significant sex differences were observed (ps [0.13).

Regional taste quality identification

As shown in Fig. 3, significant main effects of tongue region were apparent, with identification performance being higher on the front than in the back of the tongue for all stimuli except citric acid (citric acid p = 0.72, g2 = 0.00; caffeine p \ 0.0001, g2 = 0.37; sodium chloride p \ 0.0001, g2 = 0.38; sucrose p \ 0.0001, g2 = 0.63). Although subject group was not significant for any stimulus (ps [0.20), the nominal deficits between the patients and the controls were considerably larger for sodium chloride and caffeine on both the anterior and posterior regions of the tongue (Table 5).

Regional taste intensity ratings

In a similar fashion to the regional taste quality identification scores, the intensity ratings were larger on the front than on the back of the tongue, as shown in Fig. 4 (citric acid p = 0.001, g2 = 0.32; caffeine p \ 0.0001, g2 = 0.42; sodium chloride p \ 0.0001, g2 = 0.52; sucrose p \ 0.0001, g2 = 0.58). Interestingly, there was a consistent tendency for the PD patients to rate all four stimuli, relative to the controls, as stronger on the front of the tongue and weaker on the back of the tongue. The interaction between tongue region and subject group was statistically significant for sodium chloride (p = 0.042, g2 = 0.14) and nearly so for sucrose (p = 0.072, g2 = 0.11). Differences between the PD and control subject ratings were not significant, however, for either the front or the back of the tongue for any tastant (ps [0.25). Women gave significantly larger intensity ratings to caffeine than did men [respective caffeine means (SEMs) = 4.09 (0.18) and 3.10 (0.13); p = 0.025, g2 = 0.17]. This sex effect was also observed for the other stimuli, although the p values failed to reach the 0.05 level of significance (citric acid p = 0.083, g2 = 0.11; sucrose p = 0.081, g2 = 0.11, sodium chloride p = 0.14,

g2 = 0.078).

Electrogustometry

The non-parametric Wilcoxon matched-pairs signed-ranks test found no significant difference between the electrical thresholds of the PD and control subjects [respective medians (interquartile ranges) = 7.25 lA (8.84) and 6.40 lA (13.68), p = 0.74]. As was the case with most of the other measures, the thresholds did not differ signifi- cantly between men and women, as assessed by the Mann– Whitney U test [respective medians (IQRs) = 7.61 lA (22.07) and 6.40 lA (4.50), p = 0.21].

Discussion

The present study employed a variety of quantitative tests to assess whole-mouth and regional taste perception of early stage PD patients and healthy controls closely mat- ched on the basis of age, sex, and race. It determined, within the PD cohort, the influences of DRMs on the test measures and evaluated associations between these mea- sures and the side of major motor dysfunction, UPDRS scores, L-DOPA equivalency values, and dopamine trans- porter activity, as measured by SPECT imaging of [99m- Tc]TRODAT-1. The PD taste test scores were not influenced or associated with any of the dopamine-related processes that were measured, in accord with studies of several other non-motor symptoms of PD, most notably olfactory deficits [26].

A number of taste measures were clearly altered by PD. Thus, the ability to identify the saltiness of sodium chloride was significantly depressed in the whole-mouth test of the PD patients, as was the ability to detect the bitterness of low concentrations of caffeine. An unexpected finding was that, in the whole-mouth testing, the PD subjects rated, on average, the intensity of the lower concentrations of three of the four target taste stimuli as stronger than did the controls. Although this phenomenon was not statistically significant, the same trend was apparent in the regional taste test. Thus, all four tastants, when presented to the anterior tongue, were rated, on average, as stronger by the PD patients than by the controls, whereas the reverse tendency was present on the posterior tongue. However, this interaction was statistically significant only for sodium chloride, although it trended so for sucrose. These seemingly paradoxical observations receive support, in part, by the findings of others. In one study, Sienkiewicz-Jarosz and associates found that PD patients gave larger intensity ratings than did controls to a low concentration of the bitter tasting agent quinine (0.025 %) presented to the anterior tongue on filter paper strips [9]. In a subsequent study, they observed a similar phenomenon for a 1 % concentration of sucrose presented by syringe to the anterior tongue [10]. Although the PD patients of their first study exhibited lower electrical taste thresholds than controls on the anterior tongue, this finding was not replicated by them in their latter study, in accord with our negative finding on this point.

In both our whole-mouth and regional taste identification tests, the two stimuli that seemed most adversely affected by PD were caffeine and sodium chloride, particularly at the lowest concentrations that were presented. As shown in Table 2 for whole-mouth testing, the percent correct identification score differences between the PD patients and controls were 20 and 10 % at the two lowest respective caffeine concentrations; the respective differences for NaCl were 13 and 9 %. In contrast, the same values for sucrose were 1.5 and 2.6 % and for citric acid were both less than 1 %. This same phenomenon was evident in the regional taste quality identification test scores (Table 5). The basis for this apparent difference in susceptibility among the stimuli is not clear, although data from other studies support this general observation. For example, Cecchini [15] noted a PD-related deficit seem- ingly restricted to sodium chloride. Moberg et al. [13] found PD patients less likely to detect the bitter taste of PTC; in general, persons who are insensitive to PTC and related compounds are also less sensitive to NaCl [25, 26]. It is of interest that the two stimuli reported by Sienkiewicz-Jarosz et al. [9, 10] to be more intense for PD patients were quinine and sucrose. It would appear that the basis for such taste-specific differences among studies cannot be readily explained on the basis of differing transduction mechanisms, since sucrose and caffeine depend upon G-protein coupled metabotropic receptors [29–31], whereas sodium chloride, citric acid, and quinine mainly depend upon ionotropic receptors (e.g., in the case of sodium chloride, the amiloride-sensitive Na? channel) [32].

The electrogustometric threshold measure we employed did not differentiate between the PD patients and the controls. While, as noted above, most studies have found no threshold deficits in

electrical thresholds of PD patients [10] or lower thresholds in PD patients than in controls [9], one study of 75 PD patients and 74 age- and sex-matched healthy controls found significant defi- cits in PD patients on both anterior (CN VII) and pos- terior (CN IX) regions of the tongue [16]. As in our study, no influences of PD-related drug therapy were evident, although they did find that women had signifi- cantly lower thresholds than men on the anterior tongue and a trend towards this on the posterior tongue. Their test procedure differed from ours in that our forced-choice comparison was to a low stimulus rather than to a blank and that we employed a 0.5 s stimulus rather than a 1.5 s stimulus. Moreover, their criterion for determining their electrical thresholds seems somewhat unorthodox, as they noted (p. 233), ''The stimulus current was increased using a single staircase approach until the subject recognized a taste sensation; any non-taste sensation reported at lower concentrations was not recorded''. It is not clear from their publication what comprised a non-taste sensation, as electrogustometry rarely elicits clear-cut classic taste sensations [33].

Our study has both strengths and weaknesses that should be acknowledged. First, as strengths, the patients and controls were carefully selected and screened not only to optimize the correctness of the diagnoses, but to eliminate factors that may confound the test measures of interest. Second, matching of the two groups on sex, age, and race, and, inadvertently, education level, ensured that such variables were not confounding factors. Third, the taste testing was extensive, involving forced-choice electrogustometry and both whole-mouth and regional chemical testing of representatives of the four classic taste qualities. Fourth, taste function was evaluated in the same cohort of PD patients, in counterbalanced order, while they were on- and off-DRMs, eliminating between subject variance. Fifth, associations were examined between the taste test measures and UPDRS scores and SPECT imaging of the dopamine transporter within the basal ganglia. Among the weaknesses were the following. First, while we tested a sizable number of patients, our sample size was not large enough to assess the potential influences of a large number of variables and the possibility of Type I statistical errors is likely. Moreover, not all patients were able to complete both the on- and off-DRM sessions, potentially compromising the reliability of the data. Second, while every attempt was made to insure that the stimuli presented to the rear of the tongue targeted areas solely innervated by CN IX, placement of such stimuli was not always ideal and in some cases regions near the foliate papillae innervated by CN VII may also have been stimulated, potentially mitigating the contrast between CN VII and IX. Third, it would have strengthened the study to have examined chemical taste thresholds as well as the suprathreshold test measures, particularly in light of our finding that some of the deficits appeared to be confined to the lower suprathreshold concentrations that were presented. Fourth, many subjects detected the weakest currents we presented from the electrogustometer, in effect producing a clumping of the scores at the bottom of the stimulus range. This was due, in part, to the use of forced-choice testing, which results in low threshold values. An electrogustometer that presents lower levels of stimuli than those available to us is needed to avert this problem. Finally, because we were interested in the earliest sensory changes that occur in PD, our study sample contained only early stage PD patients. While this is advantageous in terms of establishing the usefulness of a measure as a biomarker for detecting early PD, a wider range of disease stages is needed to determine if an association exists between disease severity and taste dysfunction.

In summary, our study suggests that early stage PD is associated with aberrations of taste function which, in some cases, appear to depend upon the tongue regions that are evaluated [i.e., anterior (CN VII) and posterior (CN IX) regions]. We found no evidence that taste function in PD patients is influenced by dopaminergic processes. While our study found PD-related taste deficits for some stimuli at a group level, it is clear that more research is needed, possibly using different technologies, before one can determine whether taste testing can be useful, alone or in combination with other measures, as a biomarker for detecting early stage PD at the individual level.

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Figures & tables

Table 1 Characteristics of study subjects with Parkinson's disease and their matched controls

	Parkinson's disease	Matched normal controls
Age (mean ± SD)	63.1 ± 8.1	62.9 ± 8.1
Sex (m/f)	16/13	16/13
Education (mean ± SD)	16.0 ± 2.1	16.0 ± 2.6
Mini-mental state examination (mean ± SD)	29.4 ± 0.9	29.4 ± 0.8
Handedness (R/L)	27/2	27/2
Total UPDRS score (mean ± SD)	25.9 ± 10.3	NA
UPDRS motor score on DRM (mean ± SD)	16.5 ± 8.0	NA
UPDRS motor score off DRM (mean ± SD)	20.1 ± 6.6	NA
Time since diagnosis in months (mean ± SD)	16.4 ± 9.4	NA
Side of hemi-parkinsonism (number L, R and B)	17, 12, 0	NA
Hoehn and Yahr Score (mean ± SD)	1.4 ± 0.5	NA
Number of never, previous and current smokers	15, 14, 0	17, 11, 1

Table 2 Mean (SEM) percent correct whole-mouth taste quality identification scores as a function of stimulus intensity. See text for details

	Stimulus concentration 1*		Stimulus concentration 2		Stimulus concentration 3		Stimulus concentration 4		Stimulus concentration 5	
	PD	Control	PD	Control	PD	Control	PD	Control	PD	Control
Sucrose	85.34 (3.83)	83.62 (3.78)	92.24 (2.51)	94.82 (2.60)	99.14 (0.86)	97.41 (1.90)	100.00 (0.00)	90.52 (5.03)	99.14 (0.86)	98.28 (1.72)
Citric acid	69.83 (5.01)	70.69 (4.65)	74.14 (5.19)	73.28 (6.32)	81.03 (5.91)	81.90 (5.25)	79.31 (6.80)	85.34 (5.04)	71.55 (6.99)	76.72 (6.32)
NaCl	52.59 (6.62)	65.52 (6.61)	75.86 (5.88)	84.48 (4.37)	81.90 (4.95)	89.66 (3.40)	92.24 (3.31)	97.41 (1.90)	93.10 (3.01)	95.69 (2.79)
Caffeine	64.66 (7.08)	84.48 (5.47)	71.55 (6.75)	81.90 (4.95)	76.72 (6.07)	82.76 (3.94)	84.48 (5.18)	91.38 (3.11)	92.24 (3.94)	93.10 (2.75)

Stimulus concentrations are as follows: sucrose—0.08, 0.16, 0.32, 0.64, 1.28 molar [M]; sodium chloride—0.032, 0.064, 0.128, 0.256, 0.512 M; citric acid—0.0026, 0.0051, 0.0102, 0.0205, 0.0410 M; caffeine—0.0026, 0.0051, 0.0102, 0.0205, 0.0410 M. All stimuli presented in 10 mL samples

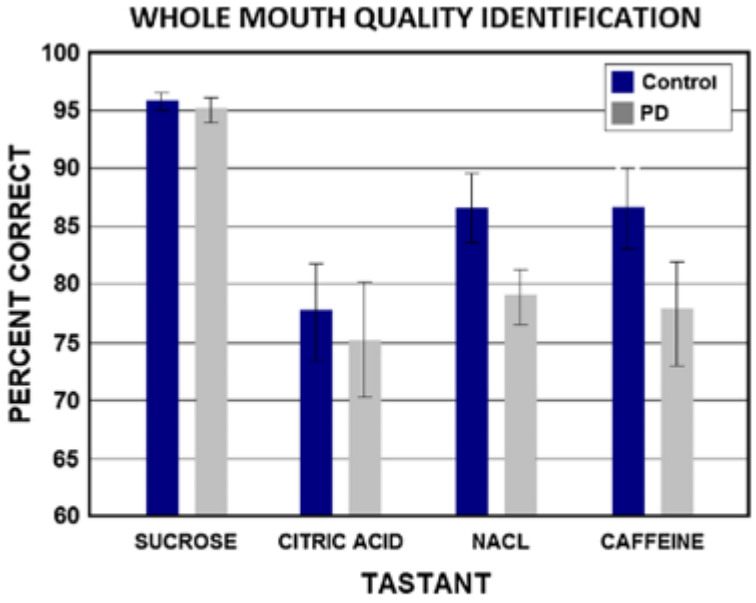

Fig. 1 Mean (SEM) percent correct performance of 29 PD patients and 29 matched controls in identifying the taste qualities of the four taste stimuli employed in this study. Data averaged over five concentrations of each stimulus. See text for details

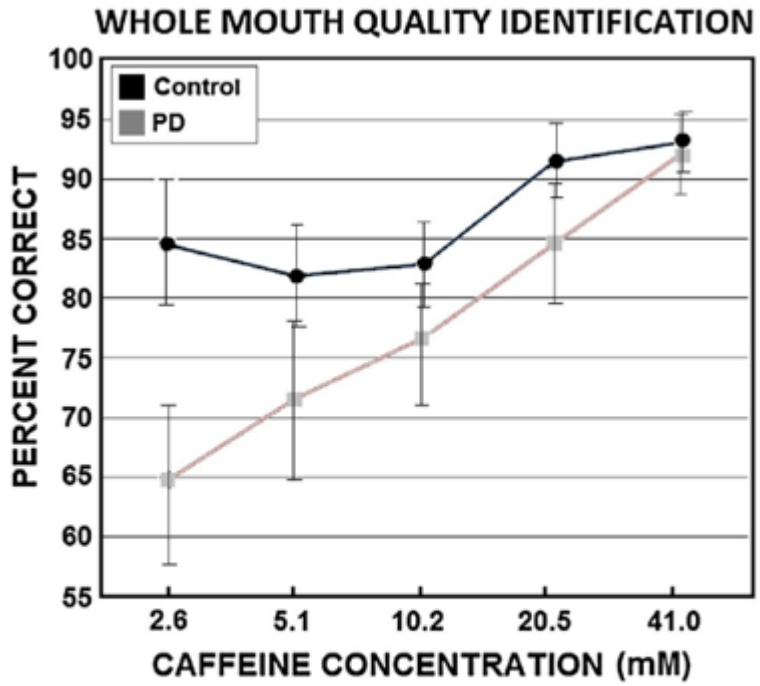

Fig. 2 Mean (±SEM) percent correct performance of 29 PD patients and 29 matched controls in identifying the bitter taste quality of caffeine at each of five stimulus concentrations. See text for details

Table 3 Mean (SEM) whole-mouth intensity ratings for the four target taste stimuli. See text for details

	Stimulus concentration 1[a]		Stimulus concentration 2		Stimulus concentration 3		Stimulus concentration 4		Stimulus concentration 5	
	PD	Control	PD	Control	PD	Control	PD	Control	PD	Control
Sucrose	3.70 (0.22)	3.42 (0.21)	4.06 (0.21)	4.05 (0.23)	5.46 (0.26)	5.40 (0.24)	5.87 (0.25)	5.97 (0.25)	6.68 (0.24)	6.69 (0.26)
Citric acid	4.63 (0.24)	4.25 (0.20)	5.23 (0.26)	4.97 (0.23)	5.72 (0.27)	5.60 (0.22)	6.57 (0.25)	6.68 (0.22)	7.10 (0.23)	7.20 (0.22)
NaCl	3.61 (0.27)	3.01 (0.22)	4.14 (0.30)	3.69 (0.25)	5.33 (0.27)	4.77 (0.23)	6.08 (0.26)	5.71 (0.21)	6.81 (0.23)	6.70 (0.23)
Caffeine	4.22 (0.32)	4.31 (0.30)	4.85 (0.30)	4.92 (0.22)	5.41 (0.25)	5.07 (0.25)	6.26 (0.25)	6.02 (0.25)	7.10 (0.24)	7.12 (0.26)

Larger numbers reflect stronger ratings

[a]Stimulus concentrations are as follows: sucrose—0.08, 0.16, 0.32, 0.64, 1.28 molar [M]; sodium chloride—0.032, 0.064, 0.128, 0.256, 0.512 M; citric acid—0.0026, 0.0051, 0.0102, 0.0205, 0.0410 M; caffeine—0.0026, 0.0051, 0.0102, 0.0205, 0.0410 M. All stimuli presented in 10 mL samples

Table 4 Mean (SEM) whole-mouth pleasantness ratings on 9-point scale for the four target taste stimuli. See text for details

	Stimulus concentration 1[a]		Stimulus concentration 2		Stimulus concentration 3		Stimulus concentration 4		Stimulus concentration 5	
	PD	Control	PD	Control	PD	Control	PD	Control	PD	Control
Sucrose	5.29 (0.21)	5.60 (0.19)	5.78 (0.16)	6.22 (0.18)	6.18 (0.23)	6.47 (0.24)	6.19 (0.31)	6.28 (0.27)	5.97 (0.35)	6.23 (0.37)
Citric acid	3.82 (0.18)	4.16 (0.12)	3.62 (0.20)	3.91 (0.19)	3.53 (0.25)	3.64 (0.21)	3.06 (0.29)	3.21 (0.22)	2.78 (0.29)	2.89 (0.27)
NaCl	4.20 (0.16)	4.50 (0.17)	3.91 (0.20)	4.48 (0.19)	3.69 (0.22)	4.21 (0.25)	3.41 (0.26)	3.78 (0.26)	3.03 (0.29)	3.34 (0.28)
Caffeine	3.66 (0.19)	3.40 (0.16)	3.55 (0.18)	3.34 (0.15)	3.23 (0.16)	3.19 (0.18)	2.69 (0.17)	2.74 (0.18)	2.24 (0.17)	2.27 (0.18)

Larger values reflect stronger pleasantness responses

Stimulus concentrations are as follows: sucrose—0.08, 0.16, 0.32, 0.64, 1.28 molar [M]; sodium chloride—0.032, 0.064, 0.128, 0.256, 0.512 M; citric acid—0.0026, 0.0051, 0.0102, 0.0205, 0.0410 M; caffeine—0.0026, 0.0051, 0.0102, 0.0205, 0.0410 M. All stimuli presented in 10 mL samples

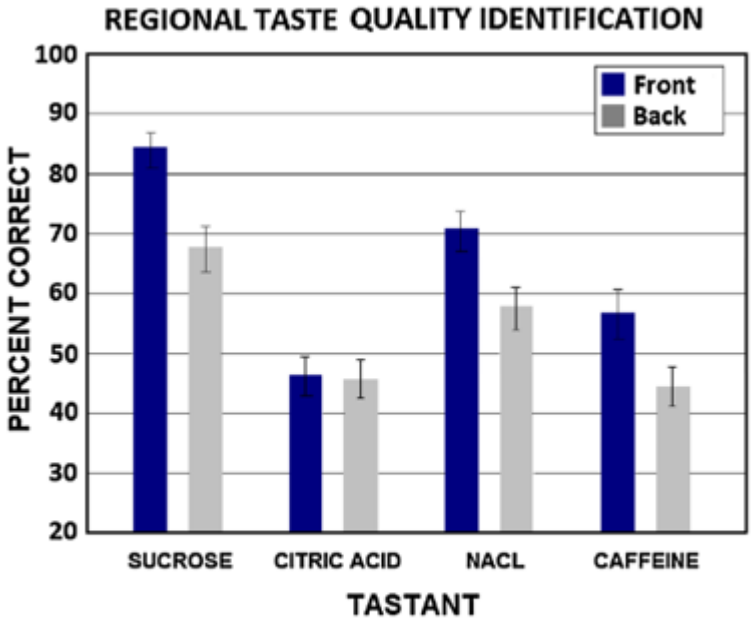

Fig. 3 Mean (SEM) percent of trials correctly identified by all study subjects as a function of taste stimulus and tongue region. See text for details

Table 5 Mean (SEM) percent correct quality identification test scores on the front and back of the tongue for the PD patient and control subjects. See text for details

Taste stimulus	Anterior tongue		Posterior tongue	
	PD	Control	PD	Control
Sucrose	84.61 (3.32)	83.99 (3.70)	67.06 (4.06)	68.36 (5.04)
Citric acid	47.90 (3.56)	46.43 (5.25)	46.85 (3.53)	45.12 (4.38)
NaCl	68.83 (4.28)	73.39 (4.10)	54.57 (4.64)	62.62 (4.87)
Caffeine	55.88 (4.63)	58.91 (5.01)	40.56 (3.64)	51.13 (4.94)

Stimulus concentrations are as follows: sucrose—0.49 molar [M]; sodium chloride—0.31 M; citric acid—0.015 M; caffeine—0.04 M. All stimuli presented in 15 11 samples equated for kinematic viscosity using cellulose (**1.53 mm^2/s)

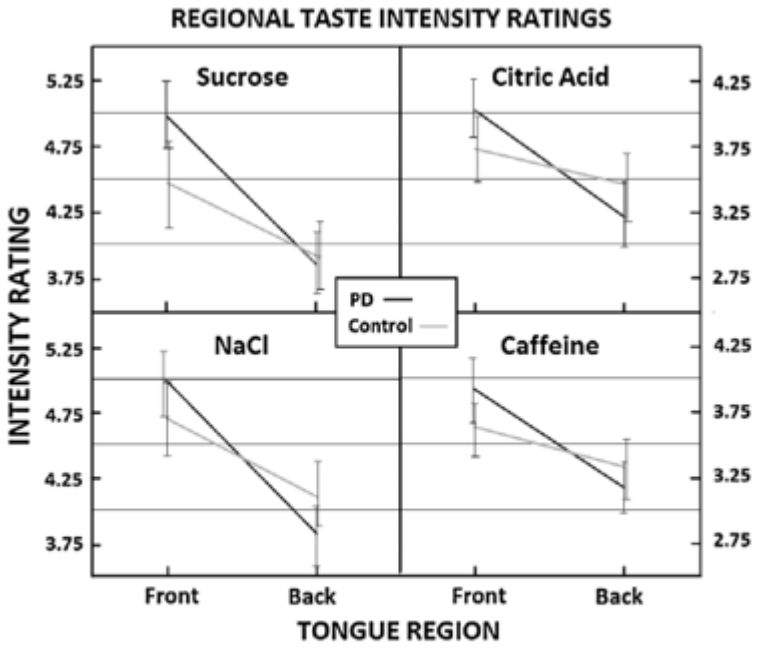

Fig. 4 Mean (SEM) taste intensity ratings given to single concentrations each of four taste stimuli to the front and back of the tongue by PD and matched control subjects. See text for details